



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Etravirine (ETR, Intelence) (Last updated April 14, 2020; last reviewed April 14, 2020)

Formulations

Tablets: 25 mg, 100 mg, 200 mg

Dosing Recommendations

Neonate and Infant Dose:

- Etravirine (ETR) is not approved for use in neonates or infants.

Child Dose:

- ETR is not approved for use in children aged <2 years. Studies in infants and children aged 2 months to 2 years are under way.

Etravirine Dosing Table for Antiretroviral Therapy-Experienced Children and Adolescents Aged 2 to 18 Years and Weighing ≥ 10 kg

Body Weight	Twice-Daily Dose
10 kg to <20 kg	100 mg
20 kg to <25 kg	125 mg
25 kg to <30 kg	150 mg
≥ 30 kg	200 mg

Adult Dose for Antiretroviral Therapy-Experienced Patients:

- ETR 200 mg twice daily with food

Selected Adverse Events

- Nausea
- Diarrhea
- Rash, including Stevens-Johnson syndrome
- Hypersensitivity with rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure

Special Instructions

- ETR tablets are sensitive to moisture; store the tablets at room temperature in the original container with desiccant.
- Area under the curve of ETR is decreased by about 50% when the drug is taken on an empty stomach. Always administer ETR with food. The type of food does not affect the exposure to ETR.
- Swallowing ETR tablets whole is the preferred means of administration and although the package insert contains instructions for dispersing ETR tablets in water or other liquids, using this administration method generally results in lower ETR exposures than swallowing tablets whole. **Children who receive dispersed ETR tablets should switch to swallowing tablets whole as soon as they are able.**

Metabolism/Elimination

- ETR is an inducer of cytochrome P450 (CYP) 3A4 and an inhibitor of CYP2C9, CYP2C19, and P-glycoprotein. It is a substrate for CYP3A4, CYP2C9, and CYP2C19.
- ETR is involved in multiple interactions with antiretroviral agents and other drugs (see text below).

Etravirine Dosing in Patients with Hepatic Impairment:

- No dose adjustment is required when using ETR in patients with mild or moderate

hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.

Etravirine Dosing in Patients with Renal Impairment:

- No dose adjustment is required when using ETR in patients with renal impairment.

Drug Interactions (see also the [Adult and Adolescent Antiretroviral Guidelines](#) and [HIV Drug Interaction Checker](#))

- Etravirine (ETR) is associated with multiple drug interactions. A patient's medication profile should be carefully reviewed for potential drug interactions before ETR is administered.
- ETR **should not be administered** with tipranavir/ritonavir, fosamprenavir/ritonavir, and unboosted protease inhibitors (PIs).
- ETR **should not be administered** with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) (i.e., nevirapine [NVP], efavirenz [EFV], rilpivirine, doravirine).
- Limited data in adults suggest that ETR may reduce the trough concentration of raltegravir (RAL),¹ but no dose adjustment is currently recommended when ETR and RAL are used together. ETR significantly reduces plasma concentrations of dolutegravir (DTG), elvitegravir/cobicistat (EVG/c), and darunavir/cobicistat.² DTG should only be used with ETR when these drugs are coadministered with atazanavir/ritonavir, darunavir/ritonavir (DRV/r), or lopinavir/ritonavir. ETR **should not be coadministered** with EVG/c.

Major Toxicities

- *More common:* Nausea, diarrhea, and mild rash. Rash occurs most commonly during the first 6 weeks of therapy. Rash generally resolves after 1 to 2 weeks on continued therapy. A history of NNRTI-related rash does not appear to increase the risk of developing rash with ETR. However, patients who have a history of severe rash with prior NNRTI use **should not receive ETR**.
- *Less common (more severe):* Peripheral neuropathy, severe rash, hypersensitivity reactions (HSRs), and erythema multiforme have all been reported. Instances of severe rash have included Stevens-Johnson syndrome, and HSRs have included constitutional findings and organ dysfunction, including hepatic failure. Discontinue ETR immediately if signs or symptoms of severe skin reactions or HSRs develop (including severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, and eosinophilia). Clinicians should monitor a patient's clinical status, including levels of liver transaminases, and initiate appropriate therapy when necessary. Continuing to use ETR after the onset of severe rash may result in a life-threatening reaction. People who have a history of severe rash while using NVP or EFV **should not receive ETR**.

Resistance

The International AIDS Society-USA (IAS-USA) maintains a [list of updated resistance mutations](#) and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

Pediatric Use

Approval

ETR is approved by the Food and Drug Administration for use in antiretroviral therapy (ART)-experienced children and adolescents aged 2 to 18 years.

Efficacy in Clinical Trials

In the PIANO study,³ ART-experienced children aged 6 years to <18 years received ETR with a ritonavir (RTV)-boosted PI as part of an optimized background regimen. At Week 24, 67% of these participants had plasma HIV RNA concentrations <400 copies/mL and 52% had HIV RNA <50 copies/mL. At Week 48, 56% of the participants had HIV RNA <50 copies/mL and a mean increase in their CD4 T lymphocyte (CD4) cell counts of 156 cells/mm³ from baseline. At Week 48, 68% of children aged 6 years to <12 years had plasma HIV RNA <50 copies/mL, while only 48% of adolescents aged 12 years to <18 years achieved a plasma viral load of <50 copies/mL.

In a retrospective study of 23 adolescents and young adults in Spain receiving ETR-based therapy, 78% of participants achieved HIV RNA <50 copies/mL at a median of 48.4 weeks of follow-up.⁴

Pharmacokinetics

In a Phase 1 dose-finding study that involved children aged 6 to 17 years, 17 children were given ETR 4 mg/kg twice daily. The study reported that two pharmacokinetic (PK) parameters—area under the curve for 12 hours post-dose (AUC_{0-12h}) and minimum plasma concentration (C_{min})—were lower than the corresponding parameters observed in adults during previous studies.⁵ However, a higher dose (ETR 5.2 mg/kg twice daily; maximum 200 mg per dose) yielded acceptable parameters and was chosen for evaluation in the Phase 2 PIANO study. Exposures (mean AUC_{0-12h}) remained lower in older adolescents than in adults and younger children, and exposures were lower in Asian participants than in either white or black participants. In the PIANO study, children and adolescents with ETR concentrations in the lowest quartile (<2,704 ng·h/mL or C_{0h} <145 ng/mL) were less likely to achieve sustained virologic responses (defined as plasma viral loads <50 copies/mL) after 48 weeks of treatment than those with ETR concentrations in the upper three quartiles.⁶

Table A. Pharmacokinetic Parameters in Children, Adolescents, and Adults Receiving Etravirine Twice Daily

Population	Mean ETR AUC _{0-12h} (ng·h/mL)	Mean ETR C _{0h} (ng/mL)
Children Aged 6–11 Years (n = 41)	5,684	377
Adolescents Aged 12–17 Years (n = 60)	4,895	325
Adults (n = 575)	5,506	393

Key: AUC_{0-12h} = area under the curve for 12 hours post-dose; C_{0h} = pre-dose concentration during chronic administration; ETR = etravirine

IMPAACT P1090 examined the PKs and safety of ETR in treatment-experienced children with HIV aged ≥2 years to <6 years.⁷ ETR was initially given at a dose of 5.2 mg/kg twice daily to a cohort of six children; however, at this dose the geometric mean ETR AUC_{0-12h} values fell below the target range of 60% of the values seen in adults. Subsequent participants were given twice-daily doses of ETR that were determined by weight band: children weighing 10 kg to <20 kg were given 100 mg per dose and children weighing 20 kg to <25 kg were given 125 mg per dose.

The tablets were swallowed whole or dispersed in liquid. The protocol-specified PK targets for ETR were achieved at these doses; the geometric mean AUC_{0-12h} was 3,504 ng·hr/mL, which was within the target range of 2,713 ng·hr/mL to 6,783 ng·hr/mL (60% to 150% of the AUC_{0-12h} value seen in adults). However, considerable intersubject variability was observed, with five of 14 participants (36%) having AUC_{0-12h} values that were below the tenth percentile for the adult AUC_{0-12h} range (<2,350 ng·hr/mL). The ETR AUC_{0-12h} values were significantly lower in children who received dispersed tablets than in children who swallowed intact tablets: 2,841 ng·hr/mL versus 10,721 ng·hr/mL, respectively (*P* < 0.0001). In light of the

increased risk of virologic failure that was observed during the PIANO study among children with lower drug exposures, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not generally recommend dispersing the ETR tablet. If ETR is administered in this fashion, the use of therapeutic drug monitoring should be considered.

Five children with HIV aged 1 year to <2 years were also enrolled in P1090. The ETR exposure in these children was lower than the ETR exposure reported in adults; the AUC_{0-12h} geometric mean ratio was 0.59 (90% confidence interval, 0.34–1.01). Virologic failure, which was defined as a confirmed viral load ≥ 400 copies/mL, occurred in three of four evaluable children by Week 24.

ETR is often combined with DRV/r for treatment of adults with HIV who have previously experienced virologic failure. Cressey et al. examined PK data from 36 adolescents and young adults receiving ETR 200 mg twice daily in combination with DRV/r 600 mg/100 mg twice daily. The PK exposures of both agents were similar to those seen in adults, although interindividual variability was high.⁸ The PKs of ETR and DRV were also studied in adolescents and young adults who received DRV/r 800 mg/100 mg once daily with either ETR 200 mg twice daily or ETR 400 mg once daily.⁹ DRV concentrations were higher when DRV was coadministered with ETR, particularly when the latter was given in doses of 200 mg twice daily. ETR exposures were lower when ETR was given with DRV/r, particularly when ETR was given twice daily; however, the authors noted that these studies had limited sample sizes. While the combination of ETR and DRV/r was effective in a small cohort of adolescents with HIV¹⁰ and in 51% of participants in the PIANO study,^{3,6} these data suggest a need for additional data on the PK interactions for ETR and other antiretroviral (ARV) agents in pediatric patients. Most notably, data is needed on regimens that do not include RTV-boosted PIs. Until such data become available, the Panel recommends using ETR as part of a regimen that includes a RTV-boosted PI.

P1090 evaluated the antiviral activity of ETR in treatment-experienced pediatric patients with HIV aged ≥ 2 years to <6 years. At baseline, the mean plasma HIV RNA viral load was approximately 247,000 copies/mL, the median CD4 count was 818 cells/mm³, and the mean CD4 percentage was 26%. At Week 24, ETR administered in combination with other ARV drugs produced a virologic response (defined as HIV RNA <400 copies/mL) in 15 of 16 evaluable participants (94%). The median increase in CD4 count from baseline to Week 24 was 298 cells/mm³, and the median increase in CD4 percentage was 5%.

Toxicity

In the PIANO study, rash and diarrhea were the most common adverse drug reactions that were deemed to be possibly related to the use of ETR. Rash (Grade 2 or higher) occurred in 13% of pediatric subjects and emerged at a median of 10 days, lasting a median of 7 days. Rash was observed more frequently in female patients (13 of 64 patients; 20.3%) than in male patients (two of 37 patients; 5.4%). In P1090, adverse drug reactions that were reported for children aged ≥ 2 years to <6 years were comparable in frequency, type, and severity to those reported for adults. Ten participants (50%) developed rashes within 4 weeks of beginning the study, but these rashes were not attributed to the use of ETR. In this study, rash occurred in 6% of female patients and 7% of male patients, and no subjects discontinued the study prematurely due to rash. Diarrhea occurred in five of 20 patients (25%).

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